Brain-Body Pathways Linking Psychological Stress and Physical Health

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Abstract
Psychological stress is thought to arise from appraisal processes that ascribe threat-related meaning to experiences that tax or exceed our coping ability. Neuroimaging research indicates that these appraisal processes originate in brain systems that also control physiological stress reactions in the body. Separate lines of research in health psychology and behavioral medicine indicate that these physiological stress reactions confer risk for physical disease. Accordingly, integrative research that cuts across historically separated disciplines may help to define the brain-body pathways linking psychological stress to physical health. We describe recent studies aimed at this goal, focusing on studies of the brain bases of stressor-evoked cardiovascular-system reactions and heart disease risk. We also outline an interpretive framework for these studies, as well as needs for next-generation models and metrics to better understand how the brain encodes and embodies stress in relation to health.

Keywords
appraisal, health, neuroimaging, stress

How does psychological stress influence physical health? This perennial question is timely for many reasons. One is that psychological stress confers risk for chronic diseases that pose the greatest burden to public health, including heart disease (Cohen, Janicki-Deverts, & Miller, 2007). Yet, although psychological stress may undermine health, we still lack a mechanistic understanding of how this might occur. A barrier to this understanding is our incomplete knowledge of how the brain generates states of psychological stress and bodily stress reactions—particularly physiological stress reactions—that may lead to physical disease or increase disease vulnerability. Critically, however, the integration of neuroimaging into human stress science is providing new opportunities to expand this knowledge. This integration is enabling us to better understand the interplay of psychological and physiological mechanisms of stress-health relationships, which can be conceptualized as involving links across at least four elements: brain appraisal systems, visceromotor outputs from the brain to organs and tissues, peripheral physiology and pathophysiology, and viscerosensory input from the body back to brain appraisal systems (Fig. 1). Here, we provide an interpretive context for recent neuroimaging studies bearing on these links. We focus on studies of disease-related cardiovascular system reactions to acute psychological stressors as example approaches to studying brain-body-health relationships.

Appraisal Systems and Psychological Stress

Brain appraisal systems constitute the first element of a pathway linking psychological stress to health-related physiology and pathophysiology. Appraisal systems encode and evaluate events and experiences (e.g., thoughts, memories, and life situations) for their meaning and significance to the individual. Specific appraisals are thought to generate states of psychological stress, particularly those associated with threats to physical, social,
and personal well-being that tax or exceed our coping ability (Lazarus, 1966; Monroe, 2008). In extension, because individuals differ in the meaning they ascribe to appraised events and their perceived coping resources, such individual differences may be linked to corresponding differences in stress reactions and health-related outcomes (Cohen et al., 2007; Lazarus, 1966; Monroe, 2008). Otherwise healthy people, for example, who appraise their life experiences as more taxing than do others exhibit higher levels of blood pressure and a faster progression of atherosclerosis, a pathophysiological determinant of heart disease (Kamarck, Shiffman, Sutton-Tyrrell, Muldoon, & Tepper, 2012).

Several mechanisms could mediate such health risks (Miller, Chen, & Cole, 2009). Of these, much historical attention has focused on the biological mechanisms by which threat appraisals might affect health via two primary stress-response systems: the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis (Lane et al., 2009). But how precisely do brain-based appraisals engage these systems and lead to physiological or pathophysiological effects on the body? Recent neuroimaging studies that measure brain and physiological activity together provide a way to address this question. Many of these kinds of studies focus on linking brain activity to changes in cardiovascular physiology mediated by the ANS (Fig. 2). Accordingly, researchers are becoming better able to characterize the human brain systems for appraisal and health-relevant stress reactions.

**Linking Appraisal to Physiology: Neuroimaging Studies of Cardiovascular Stress Reactions**

Acute psychological stressors evoke cardiovascular reactions that unfold rapidly. These reactions result from brain-based changes in ANS visceromotor outflow to the heart and vasculature—typically characterized by increases in sympathetic and decreases in parasympathetic activity.
Such changes usually lead to simultaneous increases in heart rate and blood pressure, which have long been believed to provide metabolic support for adaptive behaviors that emerge from interacting cortical and subcortical brain systems (Charvat, Dell, & Folkow, 1964). Cannon (1932) viewed these cardiovascular changes as components of “emergency reactions” that help us deal with perceived threats. In the fields of cardiovascular behavioral medicine and psychophysiology, these changes have also been viewed as arising from “central commands” in brain systems that couple peripheral physiology with effortful somatic behavior (Obrist, 1981).

Importantly, stress-related changes in cardiovascular physiology that can be measured in neuroimaging studies have been linked in epidemiological studies to heart disease risk, establishing the relevance of their brain correlates for health. Hence, individuals who exhibit metabolically “exaggerated” or prolonged stressor-evoked cardiovascular reactions (e.g., sizable and sustained rises in blood pressure and heart rate) are at risk for hypertension, heart attacks, and premature death by heart disease (Carroll et al., 2012; Chida & Steptoe, 2010).

Fig. 2. Brain regions where neural activity has been associated with cardiovascular and cardiac autonomic physiology in neuroimaging studies. As shown in panel (a), areas of the medial prefrontal cortex (mPFC; not labeled) coded in yellow indicate where activity was associated with blood pressure reactivity to a cognitive stressor (Gianaros et al., 2005). Panel (b) displays an illustrative summary of brain regions where changes in cardiovascular and cardiac autonomic activity have been associated with neural activity in existing neuroimaging studies (a complete reference list of the studies contributing to this summary is available from the authors on request). Areas in warmer colors (red and orange) correspond to brain coordinates where increases in neural activity have been associated with “pro-sympathetic” or “anti-parasympathetic” autonomic responding, as reflected by increases in heart rate (HR) and blood pressure (BP) and decreases in high-frequency heart rate variability (HF-HRV). Areas in cooler colors (blue and light blue) correspond to brain coordinates where increases in neural activity have been associated with “anti-sympathetic” or “pro-parasympathetic” responding, as reflected by decreases in heart rate and blood pressure and increases in HF-HRV. mACC = mid-anterior cingulate cortex; pgACC = pregenual anterior cingulate cortex; PAG = periaqueductal gray.
experience and expectations from the current context (Fig. 1). This is demonstrated in neuroimaging studies that manipulate appraisal-related brain activity via standardized instructions (e.g., “This is a test of your performance that predicts your real-world success”) or cognitive demand combined with failure feedback and time pressure. However, interpreting the brain changes that accompany such manipulations is problematic, as they can be resistant to tight experimental control. This is because psychological stress engages complex changes in cognitive, emotional, and physiological response systems. Thus, to enable more specific inferences about which brain systems are central to stressor-evoked cardiovascular reactivity, researchers focus on brain signals that correlate with the intensity of self-reported experiences and the patterning (e.g., magnitude) of cardiovascular reactions within and across individuals.

For example, in a series of studies focusing on heart rate reactivity, participants prepared a speech under the threat of negative social evaluation (Wager, Van Ast, et al., 2009; Wager, Waugh, et al., 2009). This stressor increased activity in several brain areas. However, the medial prefrontal cortex (mPFC)—encompassing the inner and anterior portion of the cerebral hemispheres—was the only area to show activity changes that persisted for the duration of heart rate changes. Moreover, mediation analyses showed that stressor-evoked mPFC activity (a) predicted heart rate increases on a person-by-person basis and (b) mediated heart rate reactions induced by the stressor. Notably, stressor-evoked mPFC activity linked to heart rate reactivity in these studies was decomposed into two components. The first consisted of activity increases in more dorsal mPFC areas (anterior mid-cingulate cortex [aMCC], pregenual anterior cingulate cortex [pgACC]). The second consisted of activity decreases in more ventral mPFC areas (ventromedial prefrontal cortex [vmPFC], extending into the subgenual ACC [sgACC]). The effects of both mPFC components on heart rate were, in turn, mediated by subcortical activity in the periaqueductal gray (PAG) and thalamus, areas important for stress- and threat-related ANS visceromotor control (Bandler, Keay, Floyd, & Price, 2000; Saper, 2002). Thus, these studies established a psychological stress-to-cardiovascular reactivity pathway spanning cortical (mPFC) and subcortical (PAG, thalamic) systems in humans.

In other work focusing on blood pressure reactivity, people completed demanding cognitive tasks that involved processing conflict, inhibiting overlearned responses, and receiving negative feedback under conditions of time pressure, low task control, and high task unpredictability (Gianaros & Sheu, 2009). As in the heart rate studies above, stressor-evoked blood pressure increases were associated with increases in medial prefrontal activity (aMCC, pgACC), along with increases in activity in the PAG and other subcortical ANS control areas. In earlier work also using demanding cognitive tasks (Gianaros, Van Der Veen, & Jennings, 2004), activity decreases in vmPFC were linked not only to increases in heart rate, as in the speech stressor studies above, but also to decreases in high-frequency heart rate variability (HF-HRV), a marker of parasympathetic outflow. Notably, stressor-evoked decreases in HF-HRV are linked to concurrent rises in heart rate and blood pressure (Brindle, Ginty, Phillips, & Carroll, 2014), as well as signs of heart disease risk (Gianaros et al., 2005). Importantly, animal models suggest that the mPFC responses observed in these studies likely play a causal role in mediating stressor-evoked cardiovascular reactivity (Resstel & Correa, 2006) via direct and indirect anatomical connections with subcortical ANS control centers (Gabbott, Warner, Jays, Salway, & Busby, 2005; Öngür & Price, 2000; Saper, 2002).

Together with foundational studies in this area (Critchley, 2005; Critchley et al., 2003), the above findings are converging on a picture of the brain systems underlying stressor-evoked cardiovascular reactivity (Fig. 3). Part of this picture includes generally—but not exclusively—contrasting autonomic effects linked to dorsal (e.g., aMCC/pgACC) vs. ventral (e.g., vmPFC/sgACC) mPFC areas. Dorsal mPFC areas are more often related to pro-threat/pro-sympathetic responses, whereas ventral mPFC areas are more often related to anti-threat/pro-parasympathetic responses, respectively (Fig. 2; cf. Critchley, Nagai, Gray, & Mathias, 2011). These contrasting dorsal versus ventral mPFC patterns appear similar to those seen in neuroimaging studies of stressor-evoked immune and hormonal responses (Muscattell & Eisenberger, 2012).

Although definitive homologies with nonhuman animals are unclear, the dorsal/ventral mPFC distinction found in humans may parallel distinctions between dorsal prelimbic and ventral infralimbic areas in rat mPFC, which have divergent anatomical connectivity (Vertes, 2004) and possibly opposing functions related to threat processing and responding (Quirk & Beer, 2006; Roy, Shohamy, & Wager, 2012; cf. Ulrich-Lai & Herman, 2009). In speculation, the functional nature of contrasting dorsal versus ventral mPFC patterns may correspond to a greater encoding of threat-related meaning and perhaps to stronger “central commands” to subcortical areas for greater (e.g., exaggerated or prolonged) physiological stress responding (cf. Lovallo & Gerin, 2003). Thus, a provisional view is that a functional bias in mPFC areas to encode or appraise experiences as “threatening” may represent a marker of physical (e.g., heart) disease risk.

This view, however, will undoubtedly evolve as more precise metrics are developed to quantify complex patterns of activity across cortical and subcortical visceral control systems (Table 1). Moreover, caution is warranted...
in inferring strict functional segregations of autonomic influences in the brain: There is much regional overlap and intermixing of the neural correlates of sympathetic and parasympathetic autonomic functionality (Fig. 2). This intermixing agrees with animal findings, and one consequence is that the same gross anatomical brain areas may contribute differently to cognitive, affective, and physiological stress reactions under different conditions. Furthermore, stressors can evoke complex patterns of independent, coactive, and reciprocal changes in sympathetic and parasympathetic activity (Berntson, Sarter, & Cacioppo, 1998), making it challenging to isolate unique brain correlates of each pattern of visceromotor output.

As the field advances, it will also be critical to carefully consider the subcortical systems that link stress-related cortical appraisals to downstream stress reactions. The mPFC, for instance, projects to the amygdala, PAG, and hypothalamus (among other regions), which are interconnected subcortical systems for generating threat...
responses and physiological stress reactions. Much of the human work on stress has focused on the amygdala, but its role is variable. In some work, amygdala activity relates to greater stressor-evoked cardiovascular reactivity (Gianaros & Sheu, 2009). In other work, amygdala activity is not increased by stress or related to cardiovascular reactivity or self-reported threat; rather, correlated mPFC-PAG activity predicts stressor-evoked cardiovascular reactivity, and mPFC activity predicts experienced threat (Wager, Van Ast, et al., 2009; Wager, Waugh, et al., 2009).

Such discordant findings create a discrepancy between studies emphasizing the amygdala versus the PAG in stressor-evoked cardiovascular reactivity. This paradox may be addressed by considering the related functional roles of the amygdala and PAG suggested by animal studies (McNally, Johansen, & Blair, 2011). Specifically, the PAG appears to support the encoding of primary aversive events (e.g., negative reinforcers) and provide teaching signals to the amygdala, likely in the form of prediction errors (McNally et al., 2011). The PAG also organizes patterned autonomic and behavioral responses to aversive events (Bandler et al., 2000). In contrast, the amygdala may be crucial for learning associations between aversive events (signaled in part by PAG) and other sensory cues (LeDoux, 2012). In this regard, the amygdala may trigger threat or stress responses based on learned cues, but it may not be critical for the experience of threat or fear itself.

Thus, studies that manipulate stress using sensory cues or task-related cognitive stimuli under conditions of threat (Gianaros et al., 2008) may increase or decrease amygdala activity, but studies in which the stressor is internal (e.g., in thought or memory) may not do so (Wager, Waugh, et al., 2009). Accordingly, existing findings demonstrate that the amygdala is not necessary for processing all threats or for generating stress-related physiological responses via cortical input. Instead, other systems, such as the PAG, may be equally important for such functions under some contexts. Moreover, the subcortical circuits involved in threat appraisals and linked visceral control functions are not limited to the PAG and amygdala; however, our understanding of other such circuits in humans has been limited by conventional neuroimaging acquisition and analysis methods that are not optimized for studying small subcortical brain structures (see Table 1).

**Closing the Loop: Viscerosensory Inputs to Appraisal Systems**

Stressor-evoked cardiovascular reactions may arise from cortical appraisal systems that alter peripheral physiology via interactions with subcortical systems. However, we have not yet developed a clear understanding of how appraisal-based information processing relates to visceral control loops of the body, which more directly govern peripheral physiology to influence disease vulnerability. Visceral control loops are homeostatic mechanisms that regulate our internal organs and peripheral physiological systems, such as the cardiovascular system. These mechanisms are composed of bidirectional communication pathways, in which events at one end of the loop can change events at the other end via feedforward (i.e., visceromotor) and feedback (i.e., viscerosensory) signals. The findings on cardiovascular reactivity described above, for example, can be considered from this perspective—namely, that brain appraisal systems generate and regulate health-relevant physiological stress responses by altering visceral control loops of the body.

To elaborate, heart rate and blood pressure are controlled by a visceral control loop, called the baroreflex, which maintains the momentary circulatory and metabolic requirements of the body. Specifically, the baroreflex governs blood pressure homeostasis on a heartbeat-to-heartbeat basis via (a) a viscerosensory limb that detects changes in blood pressure and (b) a visceromotor limb that adjusts sympathetic and parasympathetic outflow to the heart and vasculature to control heart rate, the force with which the heart beats, and the caliber (degree of constriction) of blood vessels (Fig. 3). Intriguingly, however, psychological stressors interrupt this visceral control loop, which is usually defined by the reciprocal coupling of heart rate to blood pressure (i.e., when blood pressure increases, heart rate decreases in a homeostatic fashion). This interruption results from a suppression of the baroreflex (Gianaros & Sheu, 2009). But how is this possible? What is the basis by which a psychological event can suppress cardiovascular homeostasis to permit blood pressure and heart rate to rise together instead of relating to each other in their typical “push-pull,” control-loop fashion?

Answers to these questions were first suggested by animal work showing that mPFC areas that presumably mediate threat appraisals in homologue areas of the human brain send anatomical projections to subcortical areas that inhibit the baroreflex, effectively taking this control loop off-line (Resstel & Correa, 2006; Verberne & Owens, 1998). This animal work was only recently extended to humans in a neuroimaging study showing that the degree of stressor-evoked baroreflex suppression related directly to the degree of stressor-evoked changes in cortical and subcortical areas previously linked to heart rate and blood pressure reactivity: the mPFC, amygdala, and PAG (Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, 2012). Another area identified was the insula (see Fig. 3), a heterogeneous cortical region important for cardiovascular control and integrating multiple
Table 1. Open Questions About Brain-Body Pathways Linking Stress and Health

1. How is chronic psychological stress represented in the brain? Chronic psychological stress—occurring over days, months, years, and longer periods of time—is clearly toxic for physical health. Moreover, converging findings from nonhuman and human neuroscience studies indicate that chronic stress can physically remodel the brain. Such remodeling is characterized by changes in neural tissue morphology (e.g., in the branching complexity of dendrites) and gross brain structure (e.g., in the localized reductions of gray- and white-matter volume and integrity). We know little, however, about how chronic stress relates to the structure or function of brain systems that are important for mediating stress appraisals, particularly in association with visceral control and health. Nor do we fully understand how acute and chronic stress processes interact at the level of the brain.

2. What brain systems mediate stress-related coping behaviors that impact health, including behaviors related to tobacco use, diet and physical activity, and alcohol consumption? Are the same putative appraisal systems of the brain that interact with visceral control loops also important for regulating such stress-related health behaviors? If so, do behavioral stress-reduction or stress-regulation interventions designed to promote health do so by affecting their functionality?

3. How are stress-related interactions between multiple visceral control loops of the body represented in the brain? Psychological stressors evoke complex and coordinated changes in multiple physiological systems, including interrelated changes neuroendocrine, autonomic, immune, and other systems. While these systems exhibit their own feedforward and feedback neuro-visceral loops, it is still not clear how the brain coordinates or registers their interactive crosstalk. Nor is it clear how their crosstalk affects the functionality of systems important for encoding and appraising psychological stressors. The field still lacks metrics that accurately characterize multisystem interactions and the bidirectional flow of integrated information between brain and body over any timescale, especially in the context of health and disease.

4. Could “big data” and pattern-classification methods (e.g., machine-learning techniques) help to better quantify and measure stress-related appraisal processes and appraisal-visceral interactions at the level of the brain? If so, might such computational methods also enable us to better link these brain-based processes and interactions to objective physical health outcomes (e.g., predicting future disease or mortality) in representative and population-based samples, which are more typical of traditional health-psychology and disease-epidemiology research?

5. Are stress and emotion or emotion-regulation processes dissociable at the level of the brain? We have an incomplete understanding of the relationships between psychological stress and emotional processes. At the level of the brain, it is becoming increasingly clear that the brain systems important for mediating emotion and emotion regulation (e.g., mPFC, amygdala, PAG) are also involved in processing psychological stressors and regulating peripheral physiological functions important for physical health. However, the overlapping and dissociable functions of brain systems related to emotion and stress remain unclear.

6. How does early life stress influence the functionality of brain systems for appraisal and visceral control in later life? Early life stress increases risk for multiple adverse health outcomes in adulthood, but we still have a poor understanding of the brain bases of this risk. Human neurodevelopmental studies are needed; such studies should include assessments of early life stress and track later changes in stress-related brain functionality and health.

7. What are the precise roles of subcortical regions in linking appraisal-related neural activity to physiological responses important for health? Most findings to date have focused on large structures, often in the cortex or subcortical telencephalon (e.g., the amygdala). However, extensive animal work relates stress and visceral control functions to changes in smaller structures, such as the hypothalamus, PAG, bed nucleus of the stria terminalis, and habenula. The relative paucity of human stress-related findings in these areas may result from artifacts in neuroimaging studies rather than true interspecies differences. As the quality and resolution of neuroimaging data improves, stress-imaging studies can reexamine the roles of these structures in human stress, emotion, and health.
bias the encoding or appraisal of future stressors or otherwise personally relevant stimuli. This bias could result from the recursive or experience-dependent updating of the meaning we ascribe to appraised events based on ongoing or prior visceral (e.g., cardiovascular) reactions. In view of these issues, our understanding of the brain systems that mediate stress appraisals and generate physiological stress responses linked to health will remain incomplete until we better account for bottom-up influences of visceral sensory information within visceral control loops.

**Summary**

Evidence from health psychology and behavioral medicine has linked the two end points of the psychological stress-health continuum. Emerging neuroimaging evidence has begun to map the brain systems that generate states of psychological stress and to link these states with visceromotor (feedforward) and viscerosensory (feedback) mechanisms important for health. Although questions remain (Table 1), this brain-body evidence may increase our ability to predict individual differences in disease risk and provide new mechanistic information on the possible origins of stress-related disease vulnerability.

**Recommended Reading**


Roy, M., Shohamy, D., & Wager, T. D. (2012). (See References). A review and meta-analysis focusing on the role of the vmPFC as a hub that links meaningful and self-relevant conceptual information about situations, contexts, and other constructs with brainstem areas important for visceral control.

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